Cardiovascular Medicine

David S. Feldman · Paul Mohacsi *Editors*

Heart Failure

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Preface

Cardiology has evolved dramatically within the past two decades due to major advances in the treatment of heart disease. At the same time, such progress has required specialization, as knowledge gains and new technological possibilities demand special focus. The European Society of Cardiology (ESC) has stayed abreast with these changes by authoring comprehensive guidelines that define an evidence-based approach not only for interventional cardiology, rhythmology, and heart failure but also for many other subfields of cardiology. Various national research groups have stated recommendations in "curricula," defining the required specialist knowledge and technical skills for subspecialties. This handbook is the first one that summarizes requested knowledge for the curricula in heart failure in Europe and the USA.

We therefore asked in a balanced manner worldwide acknowledged heart failure experts from the USA, Canada, and Europe to summarize their respective and updated knowledge.

We hope you will enjoy reading the book. Please give us your feedback, since this book is the first issue and we like to improve it at the second edition.

With best regards,

Zurich, Switzerland — Paul Mohacsi
Cincinnati, OH, USA — David S. Feldman

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Part I

Definition, Epidemiology & Etiology

Epidemiology of Heart Failure

1

Ulf Dahlström

When starting to write a book about heart failure (HF) it is important to define what you are talking about. However, first I want to present to you some historical aspects about this condition or syndrome.

1.1 Historical Aspects

The condition of heart failure (HF) has been known for many hundred years and according to Saba et al. [1] it was already mentioned in The Ebers papyrus found between the legs of a mummy in a tomb at Thebes 1862. The Ebers Papyrus is written about 1550 BC. Several of the cardiac glosses in this papyrus refer to the weakness of the heart indicating a failing heart. In one of the paragraphs it is stated about a patient "His heart was flooded or over-flooded. This is the liquid of the mouth. His body parts are all together weak". This is perhabs one of the first clinical descriptions of the term fluid overload or congestive HF. In a review by Arnold M Katz [2] he is taken us through the history of HF up to today from ancient Greek (Hippocrates) and Roman (Galen) texts via William Harvey describing the circulation in the early sixteenth century and then to Starling's demonstration of the abnormal hemodynamics found in a failing heart.

1.2 Definition of Heart Failure

During the years there have been many definitions of HF from more simplified definitions focusing on hemodynamics and defining HF as a condition where cardiac output is inadequate to meet the requirements of metabolizing tissues or inadequate in response to normal filling pressures of the heart. However this type of definition does not cover all type of patients with HF especially not well-treated patients with HF. In the 80:s the definition also included other factors such as a characteristic pattern of neural and hormonal responses besides the hemodynamic response. This type of definition was based on that activation of renin-angiotensin-aldosterone system (RAAS) as well as other hormones seemed to play an important role in the management of patients with chronic HF. At that time angiotensin converting enzyme inhibitors (ACE i:s) were used more and more in the treatment of patients with HF and the landmark study Consensus I, published 1987, was showing that treatment with ACE i:s resulted in beneficial effects in terms of reduced morbidity and mortality in patients with severe HF [3].

Today there is consensus that HF is a clinical syndrome caused by a structural or functional impairment of the heart and characterized by typical signs (e.g. pulmonary rales, peripheral oedema and elevated jugular venous pressure) and symptoms (e.g. dyspnea, fatigue and ankle swelling) associated with HF. This definition includes only patients presenting with clinical symptoms or signs associated with HF. It is also crucial to point out that it is important in all patients with HF to demonstrate the underlying cause to the cardiac abnormality. This is clearly expressed and in a similar way both in the ESC guidelines from 2016 as well as in the ACCF/AHA guidelines from 2013 [4, 5].

The cardiac abnormality can be evaluated by use of echocardiography, cardiac catheterization, cardiac magnetic resonance (CMR) technique (the best technique for assessment of volumes and ejection fraction), multi detector computed tomography, single photon emission computed tomography and radionuclide ventriculography or positron emission tomography [4]. Mostly used is evaluation by use of two-dimensional echocardiography coupled with Doppler flow studies due to availability, cost, safety and accuracy. Echocardiography provide us with information about cardiac anatomy (volumes, geometry and mass), heart valves, pericardium and cardiac function and wall motion. By mathematically calculating left ventricular ejection fraction (EF) we can estimate the cardiac function. EF can be calculated by dividing the volume ejected by the heart (stroke

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volume = end-diastolic volume (EDV) – end-systolic volume (ESV)) divided by EDV. EF depends on volume, dimensions, ventricular heart rate, valvular function, preload (the pressure of the blood on the ventricles at the end of diastole), and afterload (the pressure in the wall of the left ventricle during ejection) and the results are dependent on the measuring procedures. It is important to know that measurements of EF have methodological uncertainties as well as inter-observer variability [6].

1.3 Different Types of Heart Failure

1.3.1 Heart Failure with Reduced Ejection Fraction (HFrEF)

Due to measurement of the cardiac function calculating EF we talk today about two types of HF. First we have the old-fashioned systolic HF which we today call HF with reduced EF (HFrEF). Based on different randomized controlled studies including HF patients with a systolic dysfunction it is defined as an EF ≤ 40% [4, 5], accompanied by symptoms and signs typical of HF. Based on a number of randomized, controlled studies we also know very well how to treat patients with HFrEF. In different studies it is estimated that about 50% of the HF patients are suffering from HFrEF and the most common cause behind is a coronary artery disease (CAD) with a previous myocardial infarction (MI).

1.3.2 Heart Failure with Preserved Ejection Fraction (HFpEF)

The second type of HF is HF with preserved EF (HFpEF). This type of HF is much more difficult to define. Studies have selected patients with different cut-off values for EF as EF > 40, EF ≥ 45, EF ≥ 50 and also EF > 55%. Many of these patients did not have a normal EF (generally considered to be >50%) and therefore the term preserved is more appropriate. This diagnosis is primarily a diagnosis of exclusion. First patients with different non-cardiac causes to the clinical picture must be excluded as common comorbidities as chronic obstructive pulmonary disease, and anemia. The definition used today includes also besides symptoms and signs typical for HF also evidence of abnormal left ventricular (LV) diastolic dysfunction, which can be assessed by use of Doppler echocardiography, including evaluation of structural abnormalities as LV wall thickness, and left atrial size as well as functional abnormalities of diastolic dysfunction [4]. In the recent published ESC guidelines [4] it is also included in the definition of HFpEF that the patients should have elevated natriuretic peptides (BNP > 35 pg/ml or NT-proBNP >125 pg/ml), that is not required in the U.S. guidelines. The most common cause of HFpEF is hypertension (HT) and especially in older women. These elderly patients have a microvascular heart disease in contrast to younger men developing a more macrovascular heart disease leading to HFrEF [7]. It is wellknown that myocardial ischemia may cause diastolic dysfunction, mostly abnormalities in the relaxation phase, the most oxygen consuming part in the heart. In line with that patients presenting with risk factors as diabetes (DM) and HT and who have a stable CAD are more prone to develop HF of type HFpEF [8]. There are a number of other causes of HFpEF and the most frequent occurring conditions are heart valve diseases and renal dysfunction based on observational studies and community-based studies [9, 10]. The prevalence of HFpEF is increasing probably due to changes in population demographics and better treatment of risk factors. The prevalence has been estimated to variate between 40% and 70% dependent on which cut-off level of EF is used [11].

1.3.3 Borderline HFpEF or Heart Failure Mid-range (HFmrEF)

Today more and more are talking about the patients in the so called "grey zone" that will say patients with an EF variating between 41% and 49%. In this group of HF patients which some call HFpEF borderline or mid-range EF patients (HFmrEF) there is a mixture of patients with mild systolic dysfunction as well as patients with diastolic abnormalities and with clinical characteristics as HFpEF patients [12]. Taken into consideration that evaluation with EF is associated with some inaccuracies it seems more correct to define HFrEF as EF < 40% (as has been done) and then HFpEF as EF ≥ 50% as has been done in both the American and the ESC guidelines and on top of that evidence of diastolic abnormalities. Regarding the group with patients with EF 41–49%, this is a borderline group in the U.S. guidelines and now in the ESC guidelines a separate group of HF patients (HFmrEF). The definition required on top of diastolic abnormalities is typical symptoms and signs associated with HF and in the ESC guidelines also elevated natriuretic peptides. The definitions of HFrEF, HFmrEF and HFpEF are clearly shown in Table 1.1 [4].

1.3.4 Classifications of Heart Failure

When comparing the ACCF/AHA guidelines with the ESC guideline it is interesting to see that they use different ways to classify patients with HF. The ESC guidelines use the wellknown New York Heart Association (NYHA) classification used in most studies and dividing the severity of the patients with regard to their functional capacity and where

Table 1.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
Criteria	1	Symptoms ± signs[a]	Symptoms ± signs[a]	Symptoms ± signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: (a) Relevant structural heart disease (LVH and/or LAE), (b) Diastolic dysfunction,	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: (a) Relevant structural heart disease (LVH and/or LAE), (b) Diastolic dysfunction,

BNP B-type natriuretic peptide, *HF* heart failure, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *LAE* left atrial enlargement, *LVEF* left ventricular ejection fraction, *LVH* left ventricular hypertrophy, *NT-proBNP* N-terminal pro-B type natriuretic peptide

[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics

[b]BNP > 35 pg/ml and/or NT-proBNP>125 pg/mL

NYHA class I is a HF patient with ordinary functional capacity and no symptoms and class IV is a patient with onset of symptoms at any physical activity [13]. In the ACCF/AHA guidelines the severity of the HF is divided into four stages A-D dependent if there is any existing structural heart disease or not and if so dependent on symptoms or not. In Stage A there are no structural abnormalities and in stage B there is an existent structural heart disease without symptoms, similar to NYHA class I in the ESC guidelines (asymptomatic LV dysfunction). In stage C the severity of HF is dependent on the severity of the symptoms which are progressive and compared to the ESC guidelines similar as NYHA class II and III. Finally there is more refractory HF in stage D and in NYHA class IV. These types of classifications are also in agreement with the guidelines recommended therapy for HF. The different stages A-D selected in the ACCF/AHA guidelines are chosen regarding the difference in mortality and blood concentration of the natriuretic peptides in many studies shown to be prognostic markers [14]. The different classifications are shown in Table 1.2 [5].

Table 1.2 Comparison of ACCF/AHA stages of HF and NYHA functional classifications

ACCF/AHA stages of HF		NYHA functional classification	
A	At high risk for HF but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
		IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.
D	Refractory HF requiring specialized interventions	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

ACCF indicates American College of Cardiology Foundation, *AHA* American Heart Association, *HF* heart failure, *NYHA* New York Heart Association

1.4 Epidemiology

1.4.1 Prevalence of Heart Failure

When talking about prevalence of HF different figures were seen in different studies, which are explained by different definitions of HF used, different study populations (community based vs population based) and different age groups studied. Moreover today there are very few data regarding prevalence on patients with borderline HFpEF or HFmrEF since this is a totally new group of patients. What we know so far is that it is a mix of patients, some have systolic dysfunction and some have diastolic dysfunction and the definition is based on diastolic dysfunction as mentioned before.

Initial studies evaluating the prevalence in HF were often community-based and performed in primary health care. In many of these the diagnosis was based on clinical symptoms and signs and not on an objective evaluation of cardiac function and we know from many studies that clinical symptoms and signs are not reliable for establishing the diagnosis of HF. From a Swedish study performed in random primary health care centers, where records were carefully scrutinized in order to find how the diagnosis of HF was assessed it was found that about only 30% of the

patients had performed an echocardiographic investigation evaluating the cardiac function more objectively. In about 70% the diagnosis was set on clinical symptoms and signs, chest X-ray and electrocardiogram [15]. Recently a large Swedish study including more than 88,000 patients estimated the prevalence in Sweden to be 2.2% after adjustment for demographic composition. This was a cross-sectional investigation including all patients in the Stockholm region (population > 2.1 million inhabitants, more than 20% of the whole population in Sweden at this time) who were recorded with a primary or secondary diagnosis of HF on at least one consultation in primary health care (2003–2010) and secondary care (1997–2010) or during hospitalization [16]. The mean age for the prevalent patients in 2010 was 77± 13 years (women 80 ± 12 and men 74 ± 13). In Fig. 1.1 mortality, incidence and prevalence over time (2006–2010) are shown. How reliable are these data? The diagnosis was obtained from patients records and relies on the judgment from the responsible physician. Most of the included patients also visited secondary care or were hospitalized (83%) and there the diagnosis was confirmed by a specialist and should therefore be reliable. The validity of the Swedish National Patient Registry has been evaluated and have shown to have a high validity (82% and if primary diagnosis 95% [17]. Interesting in this study was also that it was found a weak reduction in prevalence compared with similar data from 2006 in contrast to data from Medicare beneficiaries between 1994 and 2003, where there was a slight increase in the number of HF patients suggested to be explained by improved survival [18].

Next we are focusing on population-based studies where the cardiac function has been assessed by means of an echocardiographic investigation. In one study in England including 3960 patients aged 45 years or older coming from 16 randomly selected primary care units LV systolic dysfunction was defined as an EF <40% similar to our definition of HFrEF patients. The prevalence in this study was estimated to vary between 1.8% to 3.5% and 50% of the patients were found to be asymptomatic [19]. A large cross-sectional study was performed in Portugal, the EPICA study, investigating 5434 patients evaluated by 365 general practitioners. The overall prevalence of HF in mainland Portugal was 4.36%, rising from 1.36% in the younger (25–49 years) to 16.14% in the elderly patients older than 80 years and the prevalence due to systolic dysfunction was 1.3% [20].

What we have seen so far is that the prevalence seems to increase with age and therefore it is interesting to search for studies focusing on patients with high age. One of these is The Helsinki Ageing study investigating patients aged 75–86 years and including 501 individuals. The overall prevalence in this study was 8.2%. Interesting was that most individuals (72%) had a normal ventricular function and only 2.3% had a LV systolic dysfunction [21]. Another study worth to mention is the Rotterdam study where in 7983 patients (aged ≥55 years) the prevalence was 0.9% in younger patients (55–64 years of age) increasing to 17.4% in

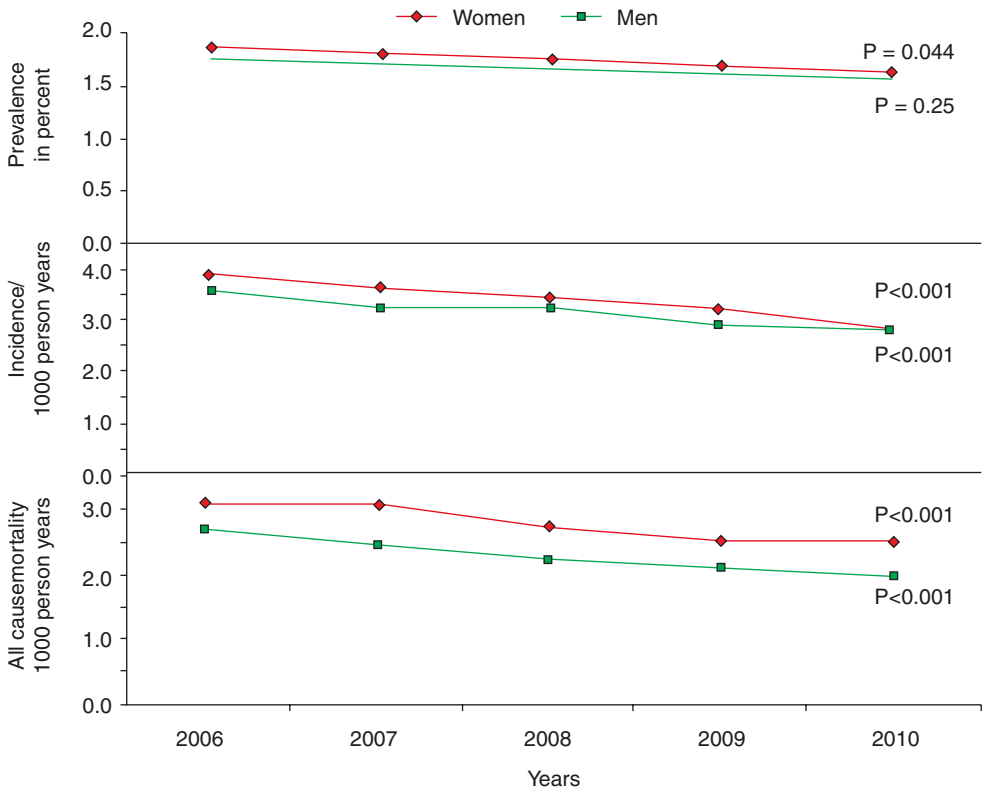

Fig. 1.1 Temporal trends in prevalence, incidence, and all-cause mortality from 2006 to 2010. The demographic composition in 2006 was used as a reference for adjustment for all values

patients older than 85 years [22]. Recently a study from Belgium investigated patients aged 80 years and older, with a mean age of 85 years and where the majority of the patients were women (63%), 567 patients were included and severe cardiac dysfunction was found in 19.3%, with systolic dysfunction in 5.8%, valvular heart disease (mostly aortic stenosis) in 10.4% and severe diastolic dysfunction in 3.1% [23]. From these studies in the elderly we see that more and more of the HF patients were having a HF with a normal EF and most of them are women.

Most of the previous studies regarding prevalence were focused on patients with systolic dysfunction, e.g. patients with HFrEF, who we know from large controlled studies how to treat. However during recent years there has been a growing interest in patients with HFpEF since it has been shown that this type of HF is very common especially in the elderly. In a review by Hogg and coworkers published 2004 a prevalence of HFpEF was found ranging from 1.5% to 4.8% with higher values in the elderly patients [24]. It was also found that the proportion of HFpEF among all HF cases lies somewhere between 40% and 71% (with a mean of 56%) and that there was an increase in the proportion of HFpEF cases in recent studies. The difference in figures is probably due to different definitions of HFpEF, study type (epidemiological study vs observational registry), practice setting (inpatients vs outpatients), and geographic location. The big differences in different studies are here shown with two studies. In the ECHOES study [19] of the general population only 1.1% had definitive HFpEF defined as a LVEF >50%, whereas in Helsinki ageing study [21] 72% had normal EF. In the Rochester study in U.S. Forty-three percent of the patients had HFpEF defined as EF > 50% [25]. In a more recent review by Lam et al. the prevalence of patients with HFpEF was found to variate between 40% and 71% (on an average 54%), thus very similar to the results found by Hogg and coworkers [12]. All this studies confirm that the prevalence increases with age. We also know from these studies that patients with HFpEF are older, more often females, and have more frequently a background of HT and DM.

In a large population based study in Olmsted county in USA it was found that the proportion of patients with HFpEF increased from 38% 1987 to 54% 2001 and this increase was only due to an increase in the number of patients with HFpEF admitted and not because of an reduction of the number of patients with HFrEF. In this study it was found that the prevalence of HFpEF relative to HFrEF is increasing at a rate of 1% per year [11]. During the same time period the number of patients with HF having HT, DM or atrial fibrillation (AF) increased in consequence with the global increase of these diseases, further pointing at the importance of HFpEF as a growing health problem and underscoring the importance of understanding the pathophysiology behind in order to find an appropriate treatment for these patients. The overall prevalence of HFpEF in the community is estimated to be 1.1–5.5% of the general population [26].

Several factors contribute to the increase of HFpEF. These factors are increased life expectancy, aging of the population, concomitant diseases cardiovascular as well as non-cardiovascular and finally better recognition (guidelines definition and improved imaging techniques). In U.S. the number of inhabitants older than 65 years have increased from 9% 1960 to 13% 2013 and projected to increase to 20% 2050, heavily contributing to the so called HF epidemic [5].

1.4.2 Incidence of Heart Failure

What about the incidence of HF. The incidence was investigated in the Hillingdon study. All incident cases were detected in a population of 151,000 covered by 82 general practices, and 99% of the patients were having an echocardiographic investigation. All the results were judged by a panel of three cardiologists making the final diagnosis. The incidence rose from 0.02/1000 per year in those aged 25–34 to 11.6/1000 in those over 85 years. The median age of investigated patients was 76 year. The study confirmed that HF is a disease of elderly [27].

In the Cardiovascular Health study, a population-based study of 5888 elderly people (mean age 73 ± 5 years), performed in USA the incidence rate was 19.3/1000 person years. The incidence of HF increased progressively across age groups and was greater in men than in women [28].

Data of incidence from primary health care are available from the UK general practice database, 696,884 individuals over age of 45 years were selected for the study and 6478 (based on records and medication) were found to have definitive HF and 14,050 with possible HF. The overall incidence of definitive HF was 9.3/1000 per year and the mean age of included patients was 77 years. The incidence was higher in men and increased with age [29]. Data from the Scottish continuous morbidity recording data set showed an overall incidence of 2/1000 per year and 22/1000 in the age over 85 [30]. In the large cross-sectional study from Stockholm, Sweden the incidence of HF was 3.7/1000 person years in women and 3.9 in men (Fig. 1.1). The mean age in this study was 77 ± 13 years [16]. According to the ACCHF guidelines the incidence of HF has been rather stable over the years with >650,000 new cases annually of HF. The incidence rate increases with age from 20/1000 in patients aged 65–69 years to >80/1000 in those over 85 years. In a recently published study, however, with data from Olmsted county in Minnesota (population about 144.248 inhabitants) evaluating incidental HF between the year 2000–2010 it was found that the age and sex adjusted incidence fell from 316/100,000 in 2000 to 219/100,000 in 2010 and the fall was greater for patients with HFrEF (−45%) than HFpEF (−27%) [31].